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08/997,464	12/23/1997	DAVID STERN	54202/JPW/SB	1340

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JOHN P WHITE
COOPER & DURHAM
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
ANGELL, JON E	
ART UNIT	PAPER NUMBER
1635	21

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/997,464	Applicant(s) STERN ET AL.	
	Examiner Jehanne Souaya	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,11,12 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,11,12 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1, 3, 4, 11, 12 and 34-37 are pending in the application.

Claim Rejections - 35 USC § 112, second paragraph

Claims 1, 3-5, 11, 12 and 34-37 were rejected under 35 USC § 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants amended claims 1, 11, 36 and 37 and cancelled claim 5. The rejection of the claims under 35 USC § 112 second paragraph are withdrawn in light of the amendment.

Claim Rejections - 35 USC § 112, first paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 11 and 12 were previously rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, No. 4, pp. 1099-1111 (also available at www.uspto.org). A summary of the rejection follows.

Claim 11 is drawn to a pharmaceutical composition which comprises a compound which inhibits neurotoxicity in a cell by inhibiting interaction between receptor for advanced glycation end product (RAGE) and mutant presenilin-2 identified by the method of claim1, and a pharmaceutically acceptable carrier. The claim encompasses a genus composed of all compounds that inhibit the interaction of RAGE and mutant presenilin-2. However, the specification does not disclose a single species compound that inhibits the interaction of RAGE and mutant presenilin-2. Therefore, the disclosure is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of a compound that inhibits the interaction of RAGE and mutant presenilin-2 at the time the application was filed. Thus, the written description requirement is not satisfied for the claimed genus. Claim 12 depends upon claim 1 and is therefore rejected for the same reason.

Furthermore, the amendment filed on April 4, 2001 has been entered as requested by the applicants in the request for continued prosecution filed June 8, 2001. However, Applicants did not respond to the office action of May 10, 2001, wherein the rejection of claims 11 and 12 under 35 U.S.C. 112, first paragraph were maintained; therefore, the rejection of claims 11 and 12 under 35 U.S.C. 112, first paragraph is maintained for the reasons previously stated in the office action of May 10, 2001, a summary of which follows.

Applicants' arguments with respect to claims 11 and 12 were carefully considered but were not deemed persuasive. It was argued that the specification is enabling for providing the claimed pharmaceutical composition *in vivo* as a transgenic mouse which has been engineered with a DNA construct encoding RAGE and a mutant PS-2 can be made by routine methods and used as a model for administering the test compound (see page 19 of applicants' Response).

With regard to the transgenic mouse models, it was argued that transgenic mouse models of Alzheimer's Disease were established in the art as of December, 1997, several of which express mutant forms of presenilins, or which co-express human presenilin and amyloid beta-protein precursor genes (references describing the transgenic mice have been supplied as Exhibits 6-9). Applicants' arguments have been considered but are not persuasive. While the prior art teaches transgenic mouse models engineered to display a phenotype associated with Alzheimer's Disease, as taught in the references provided in the Exhibits, and while it is known in the art to use transgenic mouse models in testing pharmaceutical compounds, claims 11 and 12 are directed to a pharmaceutical composition, not a method of testing a pharmaceutical composition. As stated in the previous Office actions, the specification does not disclose compounds encompassed by the claimed pharmaceutical compositions which inhibit neurotoxicity, and further, the state of the art at the time of filing teaches that providing a pharmaceutical composition for treating neurological disorders is neither routine nor predictable (see, e.g., page 6 of the Office action of 10/4/00, Paper No. 11, and pages 5-7 of the Office action of 1/3/00, Paper No. 9).

Response to Arguments

In response, Applicants have amended claim 11 to delete the phrase, "by inhibiting interactions between receptor for advanced glycation end product and mutant presenilin-2". Applicants contend that amended claim 11 obviates the rejection under 35 U.S.C. 112, first paragraph.

3. Applicant's arguments filed March 18, 2002 (paper No. 20) have been fully considered but they are not persuasive.

Amended claim 11 is drawn to a pharmaceutical composition which comprises a compound which inhibits neurotoxicity in a cell identified by the method of claim 1 and a pharmaceutically acceptable carrier. The claim encompasses a genus of compounds that are identified by the method of claim 1. However, the specification does not disclose a single species (i.e. a single compound) that has been identified by the method of claim 1. Therefore, the disclosure is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of a compound identified by the method of claim 1. Thus, the written description requirement is not satisfied for the claimed genus.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that:

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, the function of the compounds (ability to inhibit neurotoxicity) is described, but the structure of any such compound is not described.

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any compounds which have been identified by the method of claim 1 and have the ability to inhibit neurotoxicity. Therefore, the claims fail to meet the written

description requirement by encompassing compounds which are not described in the specification.

Claim 12 depends upon claim 1 and is therefore rejected for the same reason.

Claim Rejections - 35 USC § 103

4. Claims 1, 3-5, 11, 12 and 34-37 were rejected under 35 U.S.C. 103(a) as being unpatentable over Wolozin *et al.* (Science, 274:1710-1713; December 6, 1996) taken with Yan *et al.* (Nature 328:685-691, 1996). A summary of the previous rejection follows.

The claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and pharmaceutical compositions comprising the compounds identified by the method.

Wolozin teaches expressing presenilin-2 or mutant presenilin-2 (e.g. N141I) in PC12 cells and treating the cells with amyloid-β results in increased apoptosis compared to untransfected controls (see figure 4). In addition, Wolozin *et al.* disclose a method comprising a) culturing the neuronally differentiated PC12 cells in the presence or absence of a compound, i.e. pertussis toxin or amyloid-β(1–42), b) determining the level of apoptosis in the control and treated cells, and c) comparing the extent of the apoptotic activity in the cells cultured in the presence of the compound compared to cells cultured in the absence of the compound to evaluate the effect of the compound on apoptotic activity (see, e.g., page 1713, note #21).

Wolozin does not teach that the PC12 cells are transfected with a DNA sequence encoding RAGE and which is transfected in PC12 cells.

Yan teaches that enhanced expression of RAGE in Alzheimer's disease, in affected neurons, in microglial and in vasculature, is consistent with the concept that amyloid-β-RAGE interaction may contribute to neurotoxicity that results in dementia (see page 382, left column, last paragraph). Yan indicates that RAGE can mediate amyloid-β induced oxidant stress on endothelium and neuronal cells and that the stress can be prevented by blocking access to RAGE using either anti-RAGE IgG or excess soluble receptor, and further teach that expression of RAGE increases vulnerability to amyloid-β. Yan also teaches that RAGE, if present and/or upregulated in cells important in the pathogenesis of Alzheimer's' disease, could mediate toxic effects when associated with amyloid-β. Finally, Yan teaches transfection of RAGE into COS-1 cells and the use of these transfected cells in analyzing the effect of compounds on amyloid-β activity with respect to oxidant stress (see, e.g., p 688 under "RAGE and amyloid-β-induced cellular stress).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the claimed invention was made to modify the method of Wolozin *et al.* by further modifying the presenilin-2 transfected PC12 cells of Wolozin *et al.* by transfecting the cells with a vector encoding RAGE in view of the teachings of Yan *et al.* that cells transfected with RAGE are useful in studying the interaction of RAGE and amyloid-β on oxidant stress and cytotoxicity in cells.

It is pointed out that one of ordinary skill in the art would have been motivated to provide such a modified PC12 cell to use in a method of identifying inhibitors of neurotoxic compounds, in view of the teachings of Yan *et al.* that expression of RAGE in Alzheimer's disease, in affected neurons, in microglial, and in vasculature, is consistent with the concept that amyloid-β-

interaction may contribute to neurotoxicity that results in dementia. Although there was no indication in either Wolozin or Yan that an interaction between amyloid-β and presenilin-2 existed, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Wolozin *et al.* with the teachings of Yan in order to create cells that have a greater sensitivity to amyloid-β neurotoxicity than cells expressing either mutant PS2 or RAGE, for the purpose of identifying compounds that inhibit neurotoxicity.

With regard to Applicants submission that the addition of antisense molecules disclosed in Wolozin *et al.* do not render obvious the claimed invention because the teaching of Wolozin *et al.* do not make obvious the cells recited in step (a) of claim1 which overexpress RAGE and mutant PS-2. Wolozin *et al.* teaches that adding particular antisense molecules are effective in decreasing the observed apoptotic activity of PC12 cells expressing mutant PS-2 protein. It would have been obvious to an ordinary artisan at the time the claimed invention was made that adding the particular antisense molecules of Wolozin *et al.* to any cell expressing mutant presenilin-2 protein would decrease apoptotic activity of that cell, including the cells of the claimed invention which express mutant presenilin-2 and RAGE.

Response to Arguments

Applicants contend that it would not have been obvious to one of skill in the art to combine mutant PS2 with RAGE to create the present invention because the prior art references do not demonstrate or suggest any interaction between mutant PS2 and RAGE necessary for identifying and testing neuroprotective therapeutics. Therefore, applicants argue, do not provide

a suggestion of motivation to modify the reference teachings to produce the claimed invention and the claimed invention is not obvious in view of the references. In support, applicants point out that specification discloses "while mutant presenilin-2 by itself has little effect on apoptosis, cells co-transfected to express mutant presenilin-2 and RAGE showed a dramatic increase in apoptosis at Aβ concentrations of 0.3 and 1μM" (p. 23, lines 9-13 of the specification). It is also pointed out that the synergistic interaction of mutant PS2 and RAGE results in dramatically increase apoptosis (see p. 23, lines 25-27 of specification).

Applicant's arguments filed 3/11/2002 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the examiner maintains that there is motivation for one of ordinary skill in the art to combine Wolozin *et al.* and Yan *et al.*

It is pointed out that one of ordinary skill in the art would have been motivated to make such a cell for use in identifying inhibitors of neurotoxicity because Yan teaches that amyloid-β-RAGE interaction may contribute to neurotoxicity, and Wolozin teaches that cells expressing mutant PS2 demonstrate an increased sensitivity to amyloid-β. Although neither Wolozin nor

Yan indication that RAGE and mutant presenilin-2 interact, it is clear that amyloid-β at least indirectly interacts with both mutant presenilin-2 and RAGE, indicating at least an indirect interaction between RAGE and mutant PS-2 via amyloid-β. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings of Yan and Wolozin in order to create cells that have a greater sensitivity to amyloid-β neurotoxicity than cells expressing either mutant PS2 or RAGE for the purpose of identifying compounds that inhibit neurotoxicity.

In reply to the argument that cells expressing RAGE and mutant PS-2 show a synergistic interaction that results in an increased sensitivity to amyloid-β, the examiner respectfully disagrees for the following reasons.

First, although the applicants contend a synergistic interaction between mutant PS2 and RAGE, no data in the specification support such a notion. Figure 3 in the specification shows data involving control cells (i.e. untransfected cells), cells transfected with RAGE and cells transfected with RAGE and mutant PS2. The figure does not show a control wherein the cells are transfected with only mutant PS2. Without a comparison of cells expressing mutant PS2 alone versus cells expressing both mutant PS2 and RAGE, a synergistic interaction cannot be determined. Additionally, the data in Figure 3 of the specification is reported as "number of positive cells" while the data in Figure 1D of Wolozin is reported in percent of apoptotic nuclei, making it impossible to accurately to compare the two figures. Therefore, it cannot be determined if the cells expressing both mutant PS2 and RAGE show an increase in apoptosis compared to cells expressing mutant PS2 but not RAGE.

Second, applicants state "while mutant presenilin-2 by itself has little effect on apoptosis, cells co-transfected to express mutant presenilin-2 and RAGE showed a dramatic increase in

apoptosis at Aβ concentrations of 0.3 and 1μM". However, Wolozin appears to contradict this statement. Specifically, Wolozin teaches, "dPC12 cells transfected with vector (CTRL) or **wild type human PS2** (PS2wt) show low levels of apoptosis, whereas cells transfected with N141I **mutant human PS2** (PS2mut), in which Asn is mutated at position 141, show elevated levels of apoptosis and more cell detachment (see legend for Figure 1C, p. 1710) (emphasis added). It is also clear in Figure 1D that cells expressing mutant PS2 can induce apoptosis in approximately 60% of the cells (Also see Figure 4, p. 1712 for cells treated with Aβ).

It is noted that arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
May 31, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER